REMARKS

Status of Claims and Amendment

Claims 2, 4, and 5 have been amended. Claims 1, 3, 6-8, 10-12, 14-15, 20-22, 24-27, 31, and 36-37 have been canceled. Claims 2, 4, 5, 9, 13, 16-19, 23, 28-30 and 32-35 are all the pending claims in the application. Claims 2, 4, 5, 9, and 13 are rejected. Claims 2, 4, 5, 9, and 13 are objected to. Claims 16-19, 23, 28-30 and 32-35 are withdrawn as being directed to a non-elected invention.

Claim 2 has been amended to even further clarify that any of said 351 oligonucleotides "may be replaced in said set with (i) an oligonucleotide fragment of the respective oligonucleotide being replaced, which fragment is at least 15 nucleotides in length, (ii) an oligonucleotide having a sequence entirely complementary to the respective oligonucleotide being replaced, or to a fragment thereof which is at least 10 nucleotides in length, or (iii) an oligonucleotide having at least 80% identity to the respective oligonucleotide being replaced or to a fragment thereof which is at least 10 nucleotides in length." Support for the amendments to claim 2 may be found at least at page 6, lines 18-26, page 7, lines 5-11, and page 11, lines 7-12 of the specification.

Claims 4 and 5 have been amended to be dependent on claim 2.

The specification has been amended to address the objections to the specification, and to correspond the sequences listed in the Tables to the sequences provided in the Sequence Listing filed May 1, 2006.

No new matter is added.

Drawings

Applicants thank the Examiner for indicating acceptance of the drawings filed May 19, 2005.

Claim of Priority

Applicants thank the Examiner for acknowledging the claim of priority to GB Application No. 0227238.3 filed November 21, 2002, as well as receipt of the certified copy of the priority document.

Information Disclosure Statement

Applicants thank the Examiner for acknowledging the Information Disclosure Statements (IDS) filed May 1, 2006 and October 2, 2007, by returning signed and initialed copies of the PTO/SB/08A &B forms submitted therewith. The Examiner indicates that because only the abstract was provided for 15 of the listed 17 foreign patent documents, only the abstract was considered for these documents. However, the Examiner indicates that the full disclosure of the other 2 foreign documents, W0 04112589 and W0 0004187 have been considered.

Applicants respectfully request that the Examiner indicate consideration of the LIEW *et al.* document and the FUKIOKA document by returning a signed and initialed copy on the IDS PTO/SB/08A & B form submitted therewith in the next Office Communication[1].

Response To Notice to Comply

The Examiner asserts that the Sequence Listing fails to comply with C.F.R. §§ 1.821(c) and (d) because the Sequence Listing only contains SEQ ID NOs:1-501, but the specification

[1] Applicants note that Cheung, W. and Newton are not initialed because they were cited by the Examiner on the Form PTO-892.

contains sequences that are not included in the Sequence Listing. For instance, the Examiner notes that page 89, line 1 refers to SEQ ID NO 1231, and the Tables in the specification contain numerous SEQ ID NOs that correspond to nucleic acid sequences other than the 501 sequences listed in the Sequence Listing. In addition, the Examiner notes that page 166 refers to "Sequence ID 502", and page 278 refers to "SEQ ID NO: 1495" and SEQ ID NO:G6 which is an improper sequence identifier.

The Examiner requires that Applicants check the disclosure for any other nucleic acid or protein sequences and list them in the Sequence Listing with a proper SEQ ID NO.

The Examiner further points out that the specification and Sequence Listing must be amended to be compliant.

In response, Applicants note that the specification has been amended to correspond to the Sequence Listing filed May 1, 2006. In this regard, pages 72-123 and pages 124-279 have been amended to correspond to the SEQ ID NOs cited in the filed Sequence Listing May 1, 2006. Because all the sequences disclosed in the specification correspond to the respective SEQ ID NOs in the Sequence Listing, the Sequence Listing contains all the sequences disclosed in the specification, and is in compliance with C.F.R. §§ 1.821(c) and (d).

With regard to the sequences in the Tables at pages 72-121 that are indicated as "missing", reference to these "missing" sequences have been removed from the Tables at pages 82-89, 92, 97, 99, 100, 104-113, and 119-121, and from the "Note" at the end of Table 1b (page 89). Applicants note that the sequences are not missing insofar as they are referenced in the Tables, because no actual sequences were provided in the original disclosure at pages 124-279 or the Sequence Listing submitted.

Accordingly, the Sequence Listing and specification is in full compliance with 37 C.F.R. §§ 1.821-1.825.

Election/Restrictions

Applicants thank the Examiner for acknowledging Applicants' election with traverse of Group I (claims 2-5, 9 and 13) filed January 22, 2008. The Examiner asserts that Applicants' traversal is not persuasive because Ahr (Journal of Pathology (2001) volume 195, pages 312-320) teaches low density cancer blot of 588 genes, and teaches an array of more than 351 oligonucleotide probes, but less than 1000 oligonucleotide probes. Accordingly, the Examiner appears to conclude that the 588 probes of Ahr comprise at least 351 oligonucleotide probes with at least 2 nucleotides complementary to the recited SEQ ID NO. Thus, the Examiner has withdrawn claims 16-19, 23, 28-30 and 32-35 and made the restriction requirement FINAL.

In response, Applicants again note that Ahr *et al.* discloses a smaller set of probes, and does not disclose the presently claimed set of oligonucleotide probes comprising probes that are entirely complementary to the recited oligonucleotide sequences.

Nevertheless, Applicants respectfully request that claims 16-19, 22-23, 28-30, and 32-35 remain pending subject to rejoinder upon an indication of allowability of the elected claims.

Response To Objections To The Specification

The Examiner objects to the specification for the following informalities:

1. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. The Examiner points to page 40, lines 4-5 as an example of an embedded hyperlink, and requests that Applicants check the rest of the disclosure and delete the embedded hyperlink and/or other form of browser-executable code.

2. The specification page 89 states, "Sequences not available for sequence IDs in Table 1, and corresponding sequence Ids in Table 2 and 4…" The Examiner asserts that this statement appears to contradict the sequence listing which contains SEQ ID NOs. 1-501 and the sequences of pages 166 to page 279 of the specification. The Examiner asserts that it is unclear how the Table can be used to teach the sequences and yet this note states the sequences are not available.

3. The specification teaches on page 92, "Please see the note at the bottom of Table 1. Some sequences are missing." The Examiner asserts that it is unclear how the probes disclosed are informative, if the sequence is not known so that it can be differentiated from other sequences.

4. The specification teaches on page 100 a list of probes by clone ID, for example XI-8. However, the Examiner asserts that the specification does not teach how the clone ID corresponds to any of the SEQ ID NOs recited in the specification or disclosed in the Sequence Listing.

In response, and solely to advance prosecution of the present application, Applicants have made the following amendments.

With regard to item no. 1, Applicants have amended the specification to remove all embedded hyperlink and/or other form of browser-executable code.

With regard to item nos. 2 and 3, and the sequences in the Tables at pages 72-121 that are indicated as "missing", reference to these "missing" sequences has been removed from the Tables, and from the "Note" at the end of Table 1b (page 91). As discussed above, the sequences are not missing insofar as they are referenced in the Tables, because no actual sequences were provided.

With regard to item no. 4, Applicants have amended Table 3 to reference the clones to sequences in the Sequence Listing, and to remove reference to clones for which no sequence information is provided, such as clone XI-8.

Withdrawal of the grounds of objection is respectfully requested.

Response To Claim Objections

The Examiner objects to claims 2, 4-5, 9 and 13 because claim 2 contains a typographical error, *i.e.*, claim 2 recites "repective." The Examiner suggests correcting the error to recite "respective."

In response, Applicants have corrected this typographical error in claim 2.

Withdrawal of the grounds of objection is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 112 For Written Description

1. Claims 2, 4-5, 9 and 13 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection.

The Office Action asserts that claim 2 was amended to require, "any of said 351 oligonucleotides or a combination thereof may be replaced in said set...." The Office Action asserts that the specification provides support for using fragments of the oligonucleotides, but does not support replacing or substituting probes or combinations of probes. The Office Action asserts that the limitation suggests replacing a probe with a fragment, but the replacement of a single probe with a fragment does not suggest replacing multiple probes or the whole set of probes with multiple sequences.

Thus, the Office Action concludes that replacing or substituting is broader than just using a fragment and includes replacing a single probe with multiple sequences, or multiple sequences

with a single probe. The specification thus allegedly does not provide support for replacing probes or combinations of probes.

Initially, Applicants note that one of ordinary skill in the art would understand from reading the specification at, for example, page 6, lines 18-26, page 7, lines 5-11, page 11, lines 7-12, page 6 to page 8, line 33 and page 30, lines 14-24 that the claimed set of oligonucleotide probes may be selected from a set comprising each of the 351 oligonucleotides, a set comprising an oligonucleotide fragment of any one of the 351 oligonucleotides wherein the fragment is at least 15 nucleotides in length, a set comprising an oligonucleotide having a sequence complementary to any one of the respective 351 oligonucleotides, and a set comprising an oligonucleotide which is functionally equivalent to any one of the respective 351 oligonucleotides. Accordingly, pursuant to M.P.E.P. § 2163.07, one of ordinary skill in the art would readily understand and recognize from the disclosure in the specification that any of the 351 probes may be replaced with (i) an oligonucleotide fragment of the respective oligonucleotide being replaced, which fragment is at least 15 nucleotides in length, (ii) an oligonucleotide having a sequence entirely complementary to the respective oligonucleotide being replaced, or to a fragment thereof which is at least 10 nucleotides in length, or (iii) an oligonucleotide having at least 80% identity to the respective oligonucleotide being replaced or to a fragment thereof which is at least 10 nucleotides in length.

In addition, Applicants note that it appears the Office Action has misunderstood the presently claimed invention to include the possibility that a combination of the probes may replaced with, *e.g.*, just one fragment or that one probe may be replaced with multiple fragments. Applicants note that this interpretation is clearly not what was intended and is at odds with the reference to a fragment of the "respective" oligonucleotide.

Thus, solely to advance prosecution of the present application, Applicants have amended claim 2 to further clarify that the claimed set of oligonucleotide probes replace individual oligonucleotides. Reference to combinations has been removed and multiple fragments being used for replacement has been removed. The presently claimed set of oligonucleotide probes allows for any of the 351 probes to be replaced with (i) an oligonucleotide fragment of the respective oligonucleotide being replaced, which fragment is at least 15 nucleotides in length, (ii) an oligonucleotide having a sequence entirely complementary to the respective oligonucleotide being replaced, or to a fragment thereof which is at least 10 nucleotides in length, or (iii) an oligonucleotide having at least 80% identity to the respective oligonucleotide being replaced or to a fragment thereof which is at least 10 nucleotides in length.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

2. Claims 2, 4, 5, 9 and 13 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

The Office Action asserts that the claimed set encompasses 351 oligonucleotide probes, their fragments of at least 15 nucleotides in length, a sequence complementary to the sequences, or a functional equivalent such that it hybridizes under conditions of high stringency. The Office Action asserts that the structural requirements of the fragments of the oligonucleotides are set forth to be at least 15 nucleotides in length. However, the Office Action appears to assert that the sequence complementary to the respective oligonucleotide and the functionally equivalent oligonucleotide to the respective oligonucleotides do not set forth any structural limitations of a complement, a Office Action equivalent, or high stringency hybridization conditions.

Accordingly, it appears the Examiner is taking the position that the claims as presented encompass a broad range of nucleotide molecules.

Specifically, at the paragraph bridging pages 7-8 of the Office Action, the Office Action points to teachings in the specification to support the contention that when the claims are read in light of the specification, the claims encompass any nucleic acid sequence of at least 6 bases, with at least 2 bases that are complementary to the SEQ ID NO, or any sequence that remains bound 65°C when washed with 2X SSC. Also, the Office Action asserts that the specification appears to define functional equivalents in two ways, and therefore the claims are drawn to any nucleic acid sequence that can be defined as functional equivalents by either definition.

The Office Action appears to assert that the specification does not teach a representative number of fragments, complements or functionally equivalent oligonucleotides sufficient to meet the written description requirement for genus claims. In addition, the Office Action appears to assert that the fragments, complements or functionally equivalent oligonucleotides are not described with sufficient relevant identifying characteristics, e.g. other nucleotide sequences or positions within a specific gene or nucleic acid, specific features and functional attributes that would distinguish different members of the claimed genus.

The Office Action asserts that one of ordinary skill in the art cannot envision the detailed chemical structure of the encompassed nucleic acids regardless of the complexity or simplicity of the method of isolation. The Office Action appears to assert that the complementary respective nucleotide or functionally equivalent oligonucleotide are not limited by the limitation that the fragments of the claimed SEQ ID NOs be at least 15 nucleotides in length. The Office Action appears to assert that adequate written description of the complementary respective nucleotide or functionally equivalent oligonucleotides requires the nucleic acid sequence.

Thus, the Office Action asserts that the specification does not provide adequate written description to meet the breadth of the claims.

In response, Applicants note that the common structural characteristics shared by the olignonucleotide fragments, complementary sequences, and olignucleotides having at least 80% identity to the respective olignonucleotide being replaced are set forth by the SEQ ID NOs of the 351 oligonucleotides. Accordingly, as discussed above, one of ordinary skill in the art would understand from reading the specification, for instance, at page 6, lines 18-26, page 7, lines 5-11, page 11, lines 7-12, page 6 to page 8, line 33 and page 30, lines 14-24, that Applicants were in possession of the presently claimed set of oligonucleotide probes at the time the invention was made.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 112 For Enablement

Claims 2, 4-5, 9 and 13 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement.

At pages 13-22 of the Office Action, the Wands factors are set forth to support the contention that the specification does not provide an enabling disclosure to use the claimed 351 oligonucleotide probes to diagnose diseases. In this regard, the Office Action asserts that although Table 1a, Table 1b, and Table 2a each provide a list of probes for disease diagnosis, the specification does not teach what disease the probes of Table 1a, Table 1b, and Table 2a correspond to, or if the sequences recited are informative due to increased or decreased expression of the probes. The Office Action also asserts that the tables do not appear to comprise the claimed SEQ ID NOs listed at pages 14, 15, and 16 of the Office Action. The

Office Action asserts the same reasons with regard to the sequences disclosed in Figure 2b, Table 3, Table 4a and Table 9 of the specification (see pages 17-19 of the Office Action). Accordingly, the Office Action asserts that it is unpredictable to use the claimed 351 probes to diagnose disease as presently claimed. In this regard, the Office Action asserts that the art teaches that there is natural variation in gene expression among different individuals (see Cheung *et al.* Nature Genetics 33: 422-425 (2003)) and that the correlating gene expression level to any phenotypic quality is unpredictable (see Wu, Journal of Pathology 195: 53-65 (2001)). Wu is asserted to indicate that many factors may be influential to the outcome of gene expression data analysis, and that expression data may be interpreted in many ways depending on low-level considerations such as normalization and basic assumptions of normality. In addition, the Examiner asserts that Newton *et al.* (Journal of Computational Biology 8: 37-52 (2001)) teaches the difficulty in applying gene expression results, i.e., that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation.

The Office Action asserts that in order to practice the claimed invention, one of ordinary skill in the art would have to establish that a predictive relationship exists between the claimed array and disease diagnosis in a subject. However, the Office Action asserts this requires unpredictable trial and error analysis because the specification does not teach how the expressed probe set is used to diagnose disease. In this regard, the Office Action asserts that Tables la, lb, 2a, 2 b, 4 and 9 identify sequences that are informative of a disease state, such as breast cancer, Alzheimer's or Alzheimer's and breast cancer, but the specification does not teach how the combination of SEQ ID NOs diagnose Alzheimer's or breast cancer.

Accordingly, the Office Action asserts that it would be unpredictable to associate the findings of a single study with diagnosis of a disease without specific guidance as to the level of increased or decreased expression required, and as to the nucleic acid sequences or combination of nucleic acid sequences that must be identified by expression level for diagnosis.

Thus, the Office Action concludes that in light of the broad scope of the claims, the lack of guidance in the specification, the unpredictability of the art, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the claimed invention.

Initially, Applicants note that "[d]etailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention" (see M.P.E.P. §2164) "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim" (see M.P.E.P. §2164.01(b)).

Further the Board of Patent Appeals and Interferences has stated that "[t]he amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art." *Ex parte Kubin* (B.P.A.I. 2007). In other words, "[t]he fact experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P. §2164.01. The specification does not need to contain an example if the invention is disclosed in a manner as to allow one skilled in the art to practice it without undue experimentation. M.P.E.P. §2164. The absence of a working example will not by itself render the invention non-enabled, and the lack of working examples or lack of evidence that the

claimed invention works as described is insufficient grounds for lack of enablement. M.P.E.P. §2164.02. Further, "[t]he scope of enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required." M.P.E.P. §2164.03.

In the present case, large-scale gene expression analysis is well-known and routinely used in the clinical biological arts for diagnosis of disease states from clinical samples of tissues or cells originating from diseased tissues or cells[2]. As discussed in the specification, "[m]easuring changes in gene activities in cells, e.g., from tissue or body fluids is…emerging as a powerful tool for disease diagnosis" so that from "monitoring the expression of a large number of genes in cells in a test sample, it is possible to determine whether their genes are expressed with a pattern characteristic for a particular disease, condition or stage thereof." (See page 3, lines 25-37 of the specification). For instance, "several recent publications…demonstrate that gene expression data can be used to distinguish between similar cancer types. (See page 2, lines 20-26). The specification at page 37, line 25 to page 39, line 11 discloses methods commonly used in the art to generate gene expression pattern of cells in biological samples.

In addition, the difficulty that is associated with detection of disease states in asymptomatic patients for large-scale gene expression analysis is overcome by the present claimed invention because the method of the claimed invention allows for large-scale gene

[2] See Orr M.S. and Scherf U., Large-scale gene expression analysis in molecular target discovery, Leukemia 16: 473-477 (2002); and Okubo et al., Large scale cDNA sequencing for analysis of quantitative and qualitative aspects of gene expression, Nature Genetics 2: 173-179 (1992). Copies of each are attached. In accordance with M.P.E.P. § 609.05(c), the documents cited herein in support of Applicants' remarks are being submitted as evidence directed to an issue raised in the Official Action, and no fee pursuant to 37 C.F.R. 1.97 or 1.98, or citation on a FORM PTO/SB/08A & B is believed to be necessary.

expression analysis to diagnose disease states from samples of tissues or cells that are not in direct contact with a diseased tissue or cell. (See page 2, line 35 to page 5, line 37 of the specification). For instance, the analysis of gene expression of cells distant from the site of disease, such as peripheral blood collected distant from a cancer site has been described in WO98/49342.

Furthermore, the presently claimed oligonucleotide probes correspond to genes exhibiting altered expression in normal versus diseased individuals (see page 4, lines 25-33 of the specification). Further, the genes are systemically affected in a pattern characteristic of the particular disease, condition, or stage since the genes are metabolic or house-keeping genes and are constitutively, moderately or highly expressed in normal cells, i.e., cells that are not diseased cells or cells having contact with such diseased cells (see paragraph bridging pages 4-5 of the specification). The specification discloses that the claimed set of oligonucleotide probes may be immobilized on one or more solid supports that are "well known in the art and widely described in the literature" and the attachment of the nucleic acid molecules to the solid support may be done either directly or indirectly. (See pages 13 to 15, line 23). Accordingly, the claimed set of oligonucleotide probes may be used to prepare a standard diagnostic gene transcript pattern, and such pattern is used to "assess the gene expression state of a test cell to provide information relating to the organism from which said cell is derived" for the purpose of "diagnosing, identifying or monitoring a disease or condition or stage thereof in an organism." (See page 16, lines 14-23 of specification). The specification discloses the steps involved in using the claimed set of oligonucleotide probes to determine the gene transcript pattern of a cell that is indicative of the level of expression of genes to which the oligonucleotide probes bind (see page 16, line 25 to page 26, line 37, and page 22 to page 25, line 28), and the linear model equation (see page 18,

lines 1-11) to establish the pattern. Once the gene transcript pattern standard or fingerprint (standard probe pattern) is prepared for cells from an individual with a particular disease or condition, to reflect the level of transcripts which are present and correspond to each claimed oligonucleotide probe (see page 18, line 12 to page 19, line 20, and page 25, lines 23-28), the standard probe pattern is used to compare to a transcript pattern of test cells. The test gene transcript pattern is prepared in the same manner as the standard probe pattern (see page 25, line 29 to page 26, line 28), and the test gene transcript pattern is compared to the standard probe pattern in order to determine the presence or absence of the particular disease or condition (see page 26, line 19 to page 27, line 35). The data obtained from such comparison is then analyzed using basic visual representation to complex data manipulation using standard data processing and statistical methods known in the art (see page 27, line 36 to page 28, line 12).

Similarly, the elevation or depression of expression of certain markers may also be examined by looking at the standard gene transcript pattern characteristic of a disease, condition or stage (see page 32, line 30 to page 33, line 12, page 33, lines 20 to page 34, line 14) and comparing it to a test gene transcript pattern (see page 35, lines 5 to page 36, line 13). Accordingly, one of ordinary skill in the art would understand that decreased or increased expression relative to a healthy individual may be accomplished by looking for altered gene expression by generating a pattern of expression for comparison to standard patterns.

Also, with regard to the Office Action's contention that the art is negative and unpredictable regarding the many factors that may influence the outcome of gene expression data analysis, and that expression data may be interpreted in many ways depending on low-level considerations such as normalization and basic assumptions of normality, Applicants note that the raw gene expression data acquired is routinely corrected for background signals and

normalized prior to analysis using methods known in the art[3]. (See page 39, line 26 to page 40, line 25 of the specification). Such standardization of raw data collected from large-scale gene expression analysis is routinely dealt with in the art following background correction and normalization, using for example, Principal Component Analysis (PCA) as shown in Figure 1 to distinguish between Alzheimer's and non-Alzheimer's patients. (See page 40 line 26 to page 42, line 7). Other techniques routinely used in the art include standardization of gene expression data by including a subset of samples from one experimental series in the next experimental series and using a direct standardization (DS) method well known in the field of analytical chemistry (see page 42, line 8 to page 43, line 33 and Figure 1), and cluster analysis (see page 44, line 18 to page 45, line 21). As disclosed at page 45, lines 28-35, "[o]ften, the nature of the biological perturbation to which a particular sample has been subjected is known. For example, it is sometimes known whether the sample whose gene expression pattern is being analysed derives from a diseased or healthy individual. In such instances, discriminant analysis can be used for classifying samples into various groups based on their gene expression data." Accordingly, the data may be "trained" to discriminate between members and non-members of a given class using techniques known in the art such as Support Vector Machines, Nearest Neighbour, Classification trees, Voted classification, Weighted Gene voting, Bayesian classification, and Partial Least Square regression analysis. (See page 45, line 36 to page 46, line 18).

[3] See also Sherlock G., Analysis of large-scale gene expression data, Current Opinion in Immunology, 12(2): 201-205 (2000); and Carter et al., Quality assessment of microarray experiments, Clinical Biochemistry 38(7): 639-642 (2005). Copies of the abstracts are attached.

Accordingly, Applicants note that Cheung and Wu cited by the Office Action are merely concerned with identifying informative genes, which has already been performed and provided in the present invention. Similarly, Newton shows that variation exists in the level of expression, but also teaches how to identify significant variation which is more relevant to identifying genes than working with the genes once the genes have been identified.

With regard to the noise from irrelevant genes that may mask or distort the information from informative genes, the specification discloses several methods well-known and routinely used in the art to identify and select genes that are informative in microarray studies. (See page 46, lines 19-37). The specification discloses from page 27, line 36 and page 39, line 12 to page 51, line 34 how to manipulate the data. In particular, the present invention relies on the use of Partial Least Squares Regression (PLSR) to normalize and standardize the gene expression data obtained using the claimed set of oligonucleotides (see page 47, line 1 to page 49, line 12), and that statistical techniques such as Jackknife may be used to select or confirm significant variables, i.e., informative probes (see page 49, line 13 to page 53, line 35). The steps required subsequent to the identification of the relevant probes are discussed from page 51, line 1 of the specification.

With regard to the Office Action's contention that it would be unpredictable if the set of probes found in Table 2b could be used for breast cancer diagnosis in view of the existence of two different sets which are not co-extensive in scope and that one of ordinary skill in the art would not be able to predictably determine the probes required for detection of breast cancer, Applicants note that the presently claimed probes are the probes disclosed in Table 2b. The presently claimed probes have already been identified as being differentially expressed in breast cancer versus normal samples, and thus offers the selection of probes to be used in the present

invention. The specification illustrates that the claimed probes may be used for the diagnosis of breast cancer. Accordingly, because one of ordinary skill in the art would understand and is informed from reading the disclosure in the specification, which probes may be used for breast cancer diagnosis, one of ordinary skill in the art would be enabled to practice the presently claimed invention.

Furthermore, Example 3 of the specification demonstrates 345 probes used to generate the results presented in Figure 8 (page 69, lines 32-33) which provides a clustering of normal and breast cancer patients in distinguishable quadrants of that allows for the classification as normal (N) or breast cancer (B). A prediction plot is generated as shown in Figure 2, in which the disease samples appear on the x axis at +1 and the non-disease samples appear at -1. The y axis represents the predicted class membership. During prediction, if the prediction is correct, disease samples should fall above zero and non-disease samples should fall below zero. The prediction plot provided in Figure 9 using the 345 probes shows correct prediction for almost all samples. The use of the 345 probes in Example 3 is not significantly different from the use of the claimed 351 probes. Accordingly, one of ordinary skill in the art would appreciate and recognize that the use of similar set of probes of approximately the same size would be unlikely to have any significant impact on the outcome or reliability of the classification model for diagnosis.

In addition, Applicants submit herewith a Rule 132 Declaration to demonstrate the use of the claimed probes in diagnosing breast cancer, and that one of ordinary skill in the art would understand how to use the claimed oligonucleotides to diagnose diseases of interest based upon the standard and test gene transcript pattern obtained from binding to the claimed probes. Specifically, the Rule 132 Declaration provides an explanation of the use of the claimed probes in diagnosing breast cancer as shown in Figures 1 and 2 of the specification. The results shown

are similar to the results presented in Example 3 using a very similar set of probes. Furthermore, Applicants submit herewith, Meltzer published in 2001 showing that large scale gene expression was known in the art, and widely implemented so that interpretation of data obtained from large scale gene expression would not be an unpredictable obstacle (see the Introduction and Conclusions section of Meltzer). As demonstrated by Meltzer, the basic technology for data expression analysis was clearly well-established and routinely used since at least 2001.

Also, as disclosed at page 28, lines 13-24 and page 36, lines 14-27, informative probes are used to generate the standard and test patterns to diagnose disease states. Examples of such probes are disclosed, for instance, in Tables 1, 2 (to monitor breast cancer), 3, (to monitor breast cancer), 4 (to monitor Alzheimer's or Parkinson's disease) (see page 30, lines 11-28), but may also be identified using methods known in the art such as differential expression or library subtraction (see page 36, lines 28-32). In addition, the specification discloses that the informative probes may be selected based on the correlation between the informative genes and other selected informative genes under the influence of the disease, condition or stage (see page 53, line 36 to page 54, line 3). As shown in Examples 1 and 2, respectively, 139 informative probes were selected for breast cancer diagnosis and 192 informative probes for Alzheimer's disease diagnosis by training the gene expression data set of genes representing 1435 or 758 randomly picked cDNA clones for breast cancer/non-breast cancer samples, or Alzheimer's/non-Alzheimer's disease diagnosis. (See page 54, lines 4-13 and pages 58 to 66 for Examples 1 and 2).

Furthermore, unlike other large-scale gene expression techniques which select informative probes from a population of thousands of genes expressed in a cell, the informative probes selected for the presently claimed set of oligonucleotides are from a limited number of

randomly obtained genes, i.e., from a population of 1435 cDNA clones picked from a human whole blood cDNA library. (See page 55, lines 4-13). For instance, 139 informative probes have already been selected for breast cancer diagnosis (see Example 1 and Table 2).

Thus, the specification provides ample disclosure and guidance to enable one of ordinary skill in the art to use the claimed oligonucleotides, for example, in a microarray or macroarray to diagnose disease states such as cancer and/or Alzheimer's disease. One of ordinary skill in the art would be enabled to use the presently claimed set of oligonucleotide probes based upon the disclosure in the specification to perform diagnostic methods, which is entirely routine and does not require undue experimentation.

Also, Applicants note that the amendments to the specification as discussed above address the relationship between the sequences disclosed in the Tables to the sequences in the Sequence Listing because it appears the Office Action is confused with regard to how the sequences disclosed in the Tables correspond to the SEQ ID NOs in the present Sequence Listing.

Reconsideration and withdrawal of the rejection under § 112, first paragraph, is respectfully requested.

Response To Claim Rejections Under 35 U.S.C. § 102

Claims 2, 4, 9, and 13 are rejected under 35 U.S.C. § 102(b) as being anticipated by Ahr *et al.* (Journal of Pathology (2001) volume 195, pages 312-320).

It appears the Office Action is asserting the same reasons discussed above under the written description rejection. In other words, the Office Action appears to assert that the claims as presented encompass a broad range of nucleotide molecules because the sequence complementary to the respective oligonucleotide and the functionally equivalent oligonucleotide

to the respective oligonucleotides do not set forth any structural limitations of a complement, a functional equivalent, or high stringency hybridization conditions.

With respect to claims 2, 4, 9, and 13, the Office Action asserts that Ahr teaches low density cancer blot of 588 genes. The 588 probes of Ahr is asserted to contain at least 351 probes that have 2 nucleotides that are complementary to the recited SEQ ID NO. Accordingly, the Office Action asserts that Ahr teaches an array of more than 351 oligonucleotide probes, but less than 1000 oligonucleotide probes. Thus, the Office Action concludes that the 588 probes of Ahr comprise at least 351 oligonucleotide probes with at least 2 nucleotides complementary to the recited SEQ ID NOs and anticipate the present claims.

In response, Applicants note that Ahr does not explicitly or inherently disclose the presently claimed set of oligonucleotide probes.

Reconsideration and withdrawal of the rejection under § 102(b) is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

/Tu A. Phan/

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